this question to you. In your 22-year old child that is being implanted with this intraocular lens because they are minus 13 and too thin for LASIK and contact lens intolerant, what is an acceptable cell loss rate, not coefficient of variation, so that when they are 82 they still have a functioning endothelium?

What is the number? Is it .9? Is it .6? Is it 1.5? Is it 2?

DR. EDELHAUSER: Good question and it's hard to come up with a number because the thing that I think would be ideal to answer that question would be is that if we had a longitudinal study of high myopes and looked and actually measured the cell loss, I think this would be very important. Unfortunately, this is not in the literature. So the -- what you -- in order to answer that question, you know, it has jumped around between 1 to 2 percent as to where we stand with it. One can do all kinds of mathematical calculations to see, you know, how many years would the endothelial cells be depleted, half percent, one percent, two percent, and this all assumes a linear decline which I don't think is completely accurate at

this particular stage based on the new information.

So to answer your question, I don't know what the exact level would be with this without some good longitudinal data to be able to make an absolute judgment on. And I think one of the things that all of the endothelial studies suffer from is that we don't have good epidemiological data on various populations for the corneal endothelium with regard to aging and various types of subsets like high myopia for example.

DR. MACSAI: Well, given that lack of security and an absolute number, you know, I'm wary of creating another closed loop anterior chamber IOL disaster that I think most of the cornea surgeons in this room experienced. So what do you think -- I mean, is there a problem with vault and does that correlate with endothelial cell damage? We saw laser flare meter data, not fluoroscopy data, and it looked good but I've posed to the sponsors and I continue to have this concern, vault is good because cataracts are bad but does vault cause posterior chamber -- I mean, posterior iris chafing? Does it release pigment? We

don't know. We haven't looked for sample EC lines on gonioscopy.

Does that cause some chronic inflammation that over the 60-year life expectancy of this 22-year old, may effect their endothelial cells. Someone needs to, you know, provide some data from the sponsor regarding this concern.

DR. VUKICH: Well, there's two things that I think we are putting together. One would be the initial -- that could account for some initial cell loss

DR. MACSAI: And then to propose there's an increased rate of loss, there has to be some ongoing irritation to accelerate above baseline. That ongoing accelerated rate, we believe, would be consistent with the morphometric analysis. If we're going to see some sort of insult, whether it be inflammation of which we detected none, whether it would be a mechanical of which again, we would have to postulate some contact with the cornea that we simply have not observed. These chambers have remained well-formed and we have, again, not seen a mechanism by

which we can take a posterior chamber lens and equate this into ongoing corneal endothelial trauma. We would really have to propose a new mechanism for a chronic ongoing accelerated loss of endothelial cells that takes into account normal morphology and no other known cause of this accelerated loss. We believe a lot of what we're seeing here is just an extended remodeling period. We have some insult similar to what we'd expect in clear corneal cataract surgery and there is remodeling that stabilizes the population back to its, again, normal redistribution and that, we believe takes as long as three years and we simply can't see an accelerated rate. So I think projecting is difficult but we've certainly accepted the limitations of the data we have and are committed to long-term follow up. It's an important issue and I think it needs monitoring.

DR. MACSAI: Have -- you know, when you talk about long-term insult, my concern is not lens corneal touch. My concern is lens iris touch. My concern is that you know, pigment release and has the sponsor in some way separated those with the good high

vault, segregate those out, look at their flare meter, look at their angles, look at their transillumination defects, and look at their endothelial cell loss, that particular group, because I think that would help answer the question.

DR. SANDERS: Well, we do have data on three lenses were replaced because they were too long, which were the highest vault and if you look at the final endothelial cell densities, 3300, 2400, 2700. They were the highest cell densities at the later time periods so it appears that these cases are not the ones that demonstrate cell loss with time.

DR. MACSAI: But they were replaced.

DR. SANDERS: Yes, but they were replaced after a fairly long period in the eye.

DR. SUGAR: Can I ask a clarification from Marian? Are you implying that pigment release causes endothelial cell loss because I'm not aware of that?

DR. MACSAI: I'm not implying pigment release causes endothelial cell loss. I'm implying pigment release implies touch. Touch may insight chronic inflammation and may have some role in this.

I don't know. I ask the questions of the sponsor because I don't know.

DR. WEISS: Dr. McCulley and then Dr. Ho.

DR. McCULLEY: I've been around -- Jim McCulley. I've been around since prior to the beginning of clinical specular microscopy. Been through decades of frustrations of trying to listen to people make sense out of and make points based on cell density. And having listened to -- read everything that was provided, having listened to what everyone has said, quite honestly, I'm at a point where it seems to me that what you've presented at least my interpretation of it, would be that we have surgical trauma, endothelial cell loss, and no evidence for anything except continued remodeling. And no evidence for any other mechanism for continued endothelial cell loss or death other than the normal apoptotic death. So I'm not sure where, you know, one could go further with this or what we would ask you to do other than the surveillance that you're doing except to ask is there some other more sensitive way of looking for inflammation which wasn't a part of your PMA. So I'm

not even sure how fair that question is.

DR. SANDERS: With regard to the inflammation, ocular inflammation was the subject of my PhD thesis so I did quite a bit of work in this area and that's why we included in the PMA five -- I mean, the laser cell flare meter has been basically thought to be too sensitive a measure of inflammation and it's not even allowed for inflammatory studies because it's too easy to show a decrease in inflammation between groups, and five separate studies in the published literature have shown no inflammatory response after the early post-operative period with this implantable contact lens.

DR. McCULLEY: Well, then I guess what I would hope is I envision potential hours of discussion about small points relative to endothelial cell loss and cell density in something that is less than an ideal science. So I would hope that the panel would really press Hank, who is the world's expert in my experience on endothelial specular microscopy with any other issues rather than us trying to figure out what's what among ourselves. If we can have -- so I

guess my plea is -- to the panel is, please press Hank while he's here to give us the information that will be more expert than we're at to be able to generate amongst ourselves and hopefully have a more efficient discussion of this because to me this is surgical trauma remodeling.

DR. WEISS: Dr. Ho.

DR. HO: Allen Ho. But is there any evidence that this sub-clinical inflammation has a deleterious effect on the cornea?

DR. VUKICH: We have not demonstrated any subclinical information, no.

DR. HO: Is there anything in the literature?

DR. McCULLEY: I think -- Jim McCulley. They have no evidence for subclinical inflammation and depending on how you define subclinical which presumably would be what we see at the slip lamp, they've gone another step forward, don't have any. What we could do would be again, intuition. My intuition tells me what I've said. It would be intuitively to go back to some of the closed-loop AC

IOLs that actually didn't have sub-clinical, they had clinical inflammation that led to loss of endothelium, so I'm not sure that maybe in some of those eyes some of us didn't see the cell and flare that was going along with those AC IOLs but I think if you have chronic inflammation or chronic rise in intraocular pressure, there is data that suggests there is endothelial cell damage over time.

But we don't have any of that there and that's one of the things that intuitively leads me to my conclusion, we have no proposed -- we have no support for any mechanism for any continued endothelial cell loss beyond the apoptotic aging.

DR. WEISS: Yeah, I would prefer if we could keep the panel discussion in the panel discussion portion and keep the questions while the sponsor is up there because we have limited time. Do you have any other questions specifically for the sponsor?

DR. HO: I do. The only patient that had == Allen Ho -- that had severe sustainable loss of vision in this trial was a patient who had a retinal

detachment and in a group of very high myopes we would expect perhaps without intervention by natural history that you might see retinal detachment.

However, one of the predisposing factors to retinal detachment in high myopes is clearly retinal breaks and lattice degeneration. Do you have any data about number one, lattice degeneration retinal breaks pre-operatively and was indirect ophthalmoscopy part of the study procedures pre and post-operatively?

DR. VUKICH: A dilated funduscopic examination was required at several intervals throughout the follow-up period and detailed information was collected by the investigators specific to peripheral retinal findings. We don't have that collated specifically but also entry criteria did require a stable retinal exam. Any pre-existing holes or tears or retinal changes that would be considered high risk, of course, were excluded.

DR. HO: They were excluded. Stable retinal breaks were included in this or were they treated preoperatively with laser, for example?

DR. VUKICH: We do have a patient, I believe, who had -- we had one patient was treated for an acute retinal break.

DR. HO: Yeah, I think that's really important to flesh out for a potential consumer of this kind of technology because, you know, that's where you're losing an eye. However, you may not lose that eye based on your intervention. It simply may be natural history. So I think that's -- I would like to see that information. Thank you.

DR. WEISS: Do you think the optic size of 4.65 had any impact on visual acuity in younger patients who had larger pupils or is this something you didn't look at?

DR. VUKICH: Well, visual acuity and quality were two different things. The visual acuity didn't seem to have an impact in terms of the improvement in best spectacle corrected acuity. Those were the patients who actually had the most improvement quality of vision by subject of symptoms. We can stratify that by level and can provide that, yes.

DR. WEISS: So you would be able to look at the size of the pupils to see if it had any adverse effect. Dr. --

DR. VUKICH: Well, excuse me, let me qualify that by saying, pupil size measurement was not a part of this clinical exam, either preoperatively or during the course of the trial, so we could only stratify it by level of myopia, not by pupil size.

DR. WEISS: Okay, so that's an unknown factor.

DR. VUKICH: Correct.

DR. WEISS: Dr. Grimmett?

DR. GRIMMETT: A quick one for Dr. Sanders. Campbell estimated that pigment particles can be as small as one micrometer in size. Does that laser cell meter detect particles that small?

DR. SANDERS: Yes, it does. The standards that are used are in the two micron range and those are meant to be certainly large enough. One micron sized particles should be detected by the Kowan machine.

DR. GRIMMETT: You had about 20 patients

after the three-month period or so, 25 or something like that up to two years, something like that.

DR. SANDERS: Correct, and the cell measurements were essentially below one per area that was seen on average.

DR. GRIMMETT: In those 20, okay, thank you.

DR. SANDERS: Yes.

DR. SLADE: Yeah, Steve Slade, one quick point to address Dr. Macsai's concern about the vaulting, I just want to make it clear that while angle examination, gonioscopy, was not part of the exam, we certainly did slit lamp exams at multiple intervals and at no point did we ever find peripheral touch, so we were looking at grading angles in that fashion and at no point was the vaulting such that it actually caused touch or PAS.

DR. WEISS: Thank you. Dr. Mathers?

DR. MATHERS: For Dr. Edelhauser, if you're going to postulate that remodeling is the process, it might be helpful to know -- to see these cells and watch them remodel because they're not being

created. They've got to be out there. Could you help us by letting us know how many cells you like to see on a cornea to understand the remodeling process. You're looking at 93 here. What would you recommend that we try to look at if we're going to actually understand if remodeling is the issue versus cell loss on a given patient?

DR. EDELHAUSER: I think that one, it's important to do more than -- if you want right now the information, more than just central specular microscopy. Obviously, if we have these pooled cells out in the periphery, it would be interesting to see what's happening with those. I mean, and to get a larger cell number, now the -- most of the instruments that we used in specular microscopy you're limited to pretty much about four millimeters in the center, unless you really encourage the patient you can get out to maybe four millimeters off center to look at the periphery. It's not an easy measurement to obtain.

DR. MATHERS: But there's a half a million cells in that area, so --

DR. EDELHAUSER: Yeah, so I mean, one -- if one had to say predict the ideal way to really evaluate it, is I think some of the ways that we -- that article we published in the AJO is that we did take eight or nine readings across the cornea; one central, four paracentral and for far peripheral and then if you do that, you can -- and then the interesting thing when you do that, Bill, is that you find out that there's a higher percentage of corneal endothelial cells in the superior region. And similarly the German Daus all found the same thing. So you have a 16-percent increase in peripheral endothelial cells in the superior region.

DR. MATHERS: Would you recommend that -- matching that against controls as a means to obtain this understanding?

DR. EDELHAUSER: Well, if we're going to really map out what's happening in the cornea, with any type of surgical situation with remodeling one would have to do that.

DR. WEISS: Dr. Bradley has one brief question. I will ask a question and then we're going

to have a 10-minute break.

DR. BRADLEY: You might need a 10-minute break after my question. I'm bringing -- I'd like to just go back to the issue that Dr. Weiss raised a few minutes ago about pupil size. There seems to be a certain irony here. I mean, one of the motivations for the product is that there are certain people out there whose myopia level is too high although cornea too thin to perform LASIK simply because -- perform LASIK and have the standard 6.5 millimeter diameter optical zone.

The replacement product is only having potentially a 4.65 millimeter optical zone. And one of the reasons why we have a large optical zone with LASIK is because we are concerned about pupil size issues. And I'm a bit concerned that we have so little information about pupil sizes of these patients even -- we would anticipate for example, with young adults mesopic light levels that at least half of the light would be passing into the eye outside of the optical zone of the ICL.

Under those circumstances, one can only

imagine that the image quality would be very poor. Having said all that, the data seems to point that the patients are quite happy with their nighttime driving, your mesopic contrast sensitivity test with a glare source showed perfectly good results and I'm completed confused by that. I wonder if the sponsor could clarify how that could possibly happen with such a small pupil size.

DR. VUKICH: Well, we'll start by looking at pupil size. Certainly, when we developed the protocol in 1995, I don't believe that the interest or the understanding of how these pupil sizes could interact with optical quality were fully understood. That said, pupil size we neither an entry criteria nor a parameter that was measured throughout the course of the trial. I think the only way that we can answer that is to go back to the patient's satisfaction surveys and the quality of vision that they report inasmuch as the patients, in fact, didn't seem to be bothered by the theoretical concerns of an optic size smaller than their pupil. Of course, they didn't know this but what they saw they seemed satisfied with.

I understand and appreciate the concerns even with pupil size. However, there seems to be some variability in the response or the effect of the pupil size that we're understanding now with LASIK where it may not be as much of a correlation as we perhaps, intuitively may expect. So we don't understand the mechanism why a smaller optical size at the level of the lens inside the eye may not have as much influence but yet, we simply have to go back to the results and I believe that they are consistent with patient satisfaction and with the use of this device.

To speak to vision quality, there was a subset in a published report looking at vision quality in patients looking at induced aberrations and we found post-LASIK versus ICL, that the ICL patients had one-third as much spherical aberration and half as much coma. And so we certainly believe that it's at least in comparison to LASIK, probably better in that regard at least.

DR. WEISS: One last question and this is sort of a bottom line question for Dr. Edelhauser because it seems that the main concern of the panel is

the impact on the endothelium. Would you be surprised if this lens was a contributory factor in causing corneal edema in any of the patients on whom it was implanted?

DR. EDELHAUSER: At this stage, no, because the cell density of these patients were well above, you know, 23, 2400.

DR. WEISS: I should say eventually. If any of these patients eventually developed corneal edema, in conjunction with having this placed, would that surprise you or do you think that would be totally independent of having this lens placed?

DR. EDELHAUSER: Well, when you think about having a lens behind the iris and not rubbing onto the corneal endothelium, it's hard to imagine, you know, the mechanism of what would cause this -- a marked decrease in corneal endothelial cells.

DR. WEISS: So you would be -- that as a complication would be surprising to you even 20 years down the line.

DR. EDELHAUSER: Yeah.

DR. WEISS: Okay.

DR. SLADE: Just one quick thing, this lens has been implanted outside the U.S., tens of thousands of cases over 10 years and while reporting that experience is not FDA quality, I do believe we would know if this lens ever created a corneal decompensation if the patient had to have a graft and we know of none in that experience.

DR. WEISS: Thank you. We're going to take a 10-minute break and I'd ask you to be back here promptly and then we're going to go onto the FDA presentation.

(A brief recess was taken.)

DR. WEISS: Donna Lochner will be introducing the FDA presentation.

MS. LOCHNER: Thank you, Dr. Weiss. Because this is the first phakic IOL to be brought before the panel, I would like to briefly present how FDA's guidance to industry on the design of phakic IOL studies has evolved beginning with the October '98 panel meeting. In 1999 ANSI standards and later the ISO meetings began and they currently are held every six months or so. Both the ANSI and ISO standards

are expected to be submitted for voting in 2004.

Today I'll provide just the highlights of the three panel discussions and then summarize the current ANSI and ISO standards which have incorporated all the major recommendations of the panel with some minor exceptions. FDA issued a draft guidance document in 2000 and expects to issue a final guidance when the ANSI standards are finalized. So this first slide -- I think I went -- this first slide is for the October 23rd, 1998 meeting which, as I said was the first discussion by the panel and at that meeting, the panel recommended that effectiveness criteria generally followed the refractive laser guidance. For example, with respect to the uncorrected VA loss of BSCVA, and also recommended that adverse events in the first year should generally follow the IOL grid for aphakia as a starting point for the study design.

The panel recommended a sample size of 500 subjects and this was primarily because they felt that as a new indication, new technology, they should take a more conservative approach and the 500 subjects was consistent with what was originally done with IOL

aphakia studies. Further, they recommended mesopic contrast and sensitivity testing be done and mesopic pupil size measurements be done. That a questionnaire for visual complaints be administered and that pachymetry, dilated lens and fundus evaluations, topography, keratometry and gonioscopy evaluations be performed.

With regards to specular microscopy, the panel recommended a sample size to allow detection of 2.5 percent per year and they obtained this figure from the Bourne article that was referred earlier in the discussion this morning. There was a suggestion that all patients be tested but they felt that FDA should try to power the studies to detect the 2.5 percent per year. They felt PMA data was needed to three years and if there was a loss or the loss was progressing, a five-year study should be performed. With respect to lens opacities, the panel recommended a clinical grading system and three-year data be collected.

The May 12th meeting was held to receive the panel's input prior to publication of FDA's draft

guide and at that meeting, the panel generally endorsed our proposals to power the studies to be able to detect a 1.5 percent loss in the specular microscopy study per year and the 1.5 percent figure came after iterating several hypothetical annual losses from a phakic IOL taking an average endothelial cell densities at different age ranges from the literature and determining the age at which the hypothetical annual loss would result in corneal decompensation for the various age groupings. From there we assigned a standard deviation of five percent and sort of arrived at -- which was sort of arrived at as being a reasonable loss so that even young adults would be in their 70s prior to decompensation and that the sample size would still remain reasonable for these studies.

The panel endorsed this approach and also asked for data analysis to include a stratification by age. And they further recommended that the analysis look at the mean rate of loss and a frequency analysis to show the percent of patients losing greater than 10 percent over the course of the study. With respect to

lens opacities, the panel again recommended a preoperative and post-operative clinical grading system and at this meeting they also -- there was quite a bit of discussion about control group and felt that that was recommended. The panel also again emphasized gonioscopy and dilated fundus exam.

After another two years of meetings with ANSI and ISO we brought a composite of the standards to the panel but with a focused review of endothelial cell density, lens opacity and the contra-sensitivity study. We assigned primary reviewers for each of these three topics and also invited speakers to address endothelial cell design and lens opacity clinical study design issues. The panel recommended that the cell density studies be able to detect the 1.5 percent annual loss and this, again, was based upon entry criteria on cell density and acceptable density for the life of the patient. Depending upon the standard deviation, they commented that this will equate to about 200 to 300 eyes. They recommended use of a central reading center or other methods with similar precision and validity. They recommended the

three-year data was needed for the PMA and also that an intermediate measure between the two and three-year point might be needed to help to establish linearity.

Depending upon the three-year data, the panel recommended that additional two years post-marketing study may be needed. And finally, again, the frequency analysis was requested. With respect to lens opacities, again, the panel recommended a clinical rating system and the three-year data also was needed to address the issue of lens opacity and that consideration will be given to longer term at least a five-year post-marketing study. Once a PMA has been reviewed, the panel felt it was useful to look at laser flare and high resolution ultrasound for source of any opacities. And they felt that two or more lines loss with glare or one line without glare would be the level that would be considered clinically significant for any opacity.

They further recommended that contrast sensitivity testing be done on all patients to document the severity of any future opacity. With respect to the contrast sensitivity discussion, the

major recommendation that came out of that was that the panel felt a clinically significant decrease in contrast sensitivity should be set at .3 log units and again, the panel emphasized gonioscopy and further stated at this meeting that consideration should be given to collection of data post-market depending upon how the PMA data looked.

Again, as I said, all of this culminated in the current draft ANSI and ISO standards with recommendations for a three-year, 300-subject preoperative control study. Safety end points from the FDA's aphakic IOL grid are also used as control data in these standards and now I'll just briefly go through the current recommendations and the most current versions of these standards and that is that the following evaluations be performed; in corrected CVA, distance and near, BSCVA distance and near, manifest and cycloplegic refractions, a subject questionnaire, a slit lamp exam including aqueous cell and flare, gonioscopic exam, corneal edema, pupillary irregularities, iris atrophy and pigment dispersion.

These standards recommended a dilated

fundus exam, that IOP testing be performed, mesopic pupil size be measured and that pachymetry, preoperative axial length, anterior chamber duct measurement and kerotometry be performed. With respect to specular microscopy, the standards assume a 10 percent surgical loss and recommend that the studies be able to deduct a two-percent loss per year. The standards recommend that all 300 subjects be tested so that at least 200 good images would be obtained.

They recommend use of a central reading center and they recommend that 100 to 150 cells be counted. With respect to lens opacities, again the standards recommend a clinical grading system and they recommend that a change in contrast sensitivity performance from preop to each post-op visit at which an opacity is observed be performed to document any significance to the opacity. The standards recommend contrast sensitivity be performed under mesop and mesopic with glare and the sample size recommended is 61 subjects.

Now, I'd like to thank and acknowledge the

PMA review team for this application. Dr. Alexander, who is the lead reviewer for the PMA, Dr. Eydelman, the clinical reviewer, Dr. Gray who performed the statistical review, Don Calogero, our jack of all trades who performed engineering, contrast sensitivity and specular microscopy reviews. Susanna Jones reviewed the toxicology. Susan Gouge, microbiology, Charles Sawyer, patient labeling, Pam Reynolds performed the bio-research monitoring review and Vertleen Covington on the quality systems or good manufacturing practices review. And last but not least, I have to give a special thanks to Sally Thornton, who due to the expedited nature of this PMA really had to do above and beyond the amount of normal running around and we couldn't have gotten here today without her excellent support.

Now, Dr. Eydelman will present the clinical questions.

DR. EYDELMAN: Good morning. This PMA is truly precedent setting and I wanted you to be aware of it for several reasons. First of all, there are currently no phakic intraocular lenses approved in the

U.S. There are also no currently approved devices requiring intraocular surgery for correction of refractive error. Thirdly, there are no current FDA approved devices for the correction of myopia greater than 15 diopters. In addition, FDA approved IOLs for use only in adults 60 years of age and older until this year.

Currently, responses may require lowering age for indication to all adults by reference to our recent publication. This is the first time, therefore, that you're going to be considering a PMA for an IOL intended solely for implantation in young adults. As you heard, this PMA received an expedited review status. That truly meant much shorter turnaround time for both the sponsor and us. To make a point of it, I want you to be aware that the last major clinical amendment wasn't received by FDA till September 3rd.

As a result of all this, I haven't been able to receive the sponsor's final panel presentation until today, so please forgive any redundancies that I might have in my presentation. As you have all

seen, this was a very large PMA with numerous analysis and I will not try to summarize all of it. I'm merely trying to bring your attention to some information which is relevant to the questions that we ask for your consideration.

Regarding lens opacification, there were five eyes in the whole PMA that developed nuclear opacities of two plus at the LOCS scale at two to three years. There were 14 cases of ASC opacities of trace or more. Eleven of them occurred at or before the six months and three cases at one year to 26 months post-op. In view of these, do you believe that the three-year follow up is sufficient to establish a lens opacification profile associated with this device? If not, what is your recommendation?

Eleven out of the 14 cases of ASC appeared at or before the six-month visit suggesting surgical trauma. Combining surgical experience with V3 and V4 models, 50 percent of 87.5 percent if you exclude the problematic site number 15, of early ASC cases occurred within the first eight surgical cases. In the Canadian trial performed by three inexperienced

surgeons, 22.5 percent of cases developed ASC opacification.

The Dominican Republic study which was performed under supervision of a surgical proctor, demonstrated a rate of 4.8 percent. In light of these findings, do you believe surgeon experience to be an important factor in ASC development, secondary to surgical trauma? If yes, do you believe that future users of this lens should be required to undergo special training?

Vault measurements in the study were clinical estimates comparing the slit lamp appearance of the corneal thickness to the interval centrally between the crystalline lens and the ICL. Five hundred micron corneal thickness was assumed for conversion from a percentage of corneal thickness to microns. All measurements in an individual case at every visit were averaged to derive at a vault measurement. So as you can see, it was not a very precise measurement estimate. However, it was done.

Patients were graded as having poor vault if investigators consistently graded the space

between ICL and crystalline lens as less than 10 percent of the central corneal thickness and that equated to about 50 microns. Twenty-four cases of the V4 cohort with this technique were determined to have poor vault, 16.7 percent of them or four out of 24 V4 cases with poor vault, subsequently developed ASC opacification in contrast only two percent of cases with good vault had ASC.

All three cases of significant ASC opacification of late onset defined as greater than six months in V4 cohort were in the eyes with poor vault. In V3 cohort, 41 percent of cases with poor vault developed ASC versus nine percent of cases with good vault. Gonvers, et al, in his recent publication further supported the relationship of vaulting to cataract information. In the PMA the sponsor recommended replacement of the ICL only in cases of poor vault that exhibited early ASC in areas of ICL touch in subjects with UCVA worse than 20/50. Do you agree with this recommendation? If not, what would you recommend?

In the clinical trial, sizing was

determined by the horizontal white-to-white and ACD, anterior chamber depth measurements. Inherent measurement error associated with caliper measurements was judged by the sponsor to be plus or minus .1 millimeter. Anterior chamber depths in the study was measured by ultrasound, Orbscan and IOL master. From the literature review, the sponsor concluded that results may differ by as much as .3 millimeters between different measurement methods.

Our own literature review revealed lack of correlation of white-to-white measurements and the sulcus-to-sulcus dimension. We also believed that the literature shows that none of the external measurements, including anterior chamber depth and axial length, have been able to accurately predict internal ocular dimensions. The sponsor believes that this literature evidence currently available is anecdotal and they further point out that all the safety and efficacy data available were obtained with a current sizing algorithm based on white-to-white and ACD measurements.

It's interesting to note that looking at

the distribution of the ICL implanted, 50 percent were performed with 12.5 millimeters, versus 7.6 percent was 11.5 millimeter lens. In the overall PMA cohort, 1.5 percent of the lenses were replaced due to inappropriate sizing. Do you believe that the method currently recommended by the sponsor for determination of the overall diameter of the ICL to be inserted is appropriate? If not, what do you recommend?

As you heard previously, we asked the sponsor to break up their cohort into four refractive groups. Fifteen to 20 diopter group contained 31 eyes at three years. I want to make sure that you're aware that while preliminary discussion for refractive laser guidance for myopia greater than seven diopters was held a the '97 panel meeting. There was no consensus reached on several issues and therefore, there is no currently available guidance for acceptable safety and efficacy outcomes for high myopes after refractive surgery. For eyes with MRSE greater than 15 diopters, in the ICL cohort, there were 3.8 percent or two eyes that lost greater than two lines, 3.8 percent that lost 2 lines and 17.3 percent that lost 1 line. If

you calculate it out, it turns out that at 15 diopters of myopia, magnification factor account for a one-line loss being equivalent to a two-line loss. Therefore, we ask the sponsor to include that in the analysis of their high myopia group.

Thus, if you add it up, total loss of one line or greater was 25 percent for the small cohort. Some additional safety outcomes for these eyes were retinal detachment at 3.8 percent, ASC opacification of 5.8 percent and as of 9/15, only -- the sponsor informed us that only one eye of these was clinically -- had clinically significant ASC and that is 1.9 percent. Clinically significant nuclear cataract in 7.7 percent, ICL removal/cataract extraction performed in 3.8 percent and again, 3.8 percent had an increase of greater than two diopter cylinder.

As you heard, currently limitation of ICL power is minus 20 diopters. Inadvertently a lot of eyes with MRSE greater than 15 diopters were targeted for under-correction. Eleven point five percent of them were targeted for greater than three diopters, 28.8 for greater than two and 65.4 for greater than

one. Looking at predictability, 23.3 percent had accuracy within half diopter, 53.3 was within one diopter. Combining the targeted under-correction was a predictability that you saw resulted in rather large range for resultant MRSE for this group at three years. As you can see, it ranged from minus .85 diopters to plus .5 with 10 percent of the eyes ending up greater than four diopter myopia, 26.6 greater than three diopters.

Looking at all eyes with preop MRSE greater than 15 diopters 38.7 percent of them were able to achieve 20/40 or better. There were no eyes available that were targeted for emmetropia and had preop of 20/20 or better. While all eyes in this sub-group were -- while there were no eyes that were -- there were no patients that were unsatisfied, looking at very extremely satisfied patients, you see that for the group of greater than 15 diopters, the satisfaction percentage drops somewhat to 75 percent.

Does the safety and efficacy data for eyes with preoperative myopia of greater than 15 to 20 diopters support approval of this refractive range?

If approval for eyes with preoperative MRSE greater than 15 to 20 is recommended, is the term "correction of" as it relates to this refractive range, appropriate in the indication statement? If not, what alternative term do you recommend?

Any time we at FDA consider risk benefit analysis for each of the refractive groups, we have to consider two factors. First, is a safety and efficacy profile for each refractive group with the device in question. In addition, we look at safety and efficacy profile for the currently approved or alternate devices available; in this case, glasses, contacts, LASIK, for each of the refractive groups? With this in mind, does the safety and effectiveness outcomes support approval of STAAR ICL for the eyes with the following preoperative MRSE, minus 3 to minus 7, greater than 7 to 10, and from greater from 10 to 15 diopters? Twenty patients in overall PMA cohort required treatment other than IOP-lowering meds in the early post-op period. Seventeen of them requiring additional irodotomies, and three requiring additional irrigation/aspiration procedure. In these 20 eyes,

IOP ranged as high as 65, with IOP spikes observed between one and 21 days post-op. Most of them, however, were seen in one to two days post-op.

Incidents of early post-op spikes was stratified by study site and was shown to range between zero to 20 percent. The differences were not found to be statistically significant. Do you believe that specific recommendations regarding early post-op follow up are needed in the labeling? I want to bring your attention to the fact that the labeling you currently have is not -- did not undergo final FDA's review. We always correct all the inconsistencies. Patient symptoms and quality of vision assessment stratified by refractive groups would automatically be included. Demographics is always included.

What we are asking your input on is issues unique to ICL that need to be communicated in physician and patient labeling, possibly as a warning or precaution. In addition, we're asking you to consider issues that will be common to all phakic IOLs, such as possible requirement for exclusion of subjects with low endothelial cell density as a

function of age. This would be consistent with ANSI PIOL draft standards recommendation for clinical studies. It would, however, imply access to specular microscope for all implanting surgeons.

In addition, recommendations for gonioscopy and mesopic pupil size assessment preop and post-op in all patients. This is consistent, once again, with our standards recommendation for all clinical studies. Overall, we want to know what additional labeling recommendations do you have. Now, I would like to introduce Dr. Gerry Gray who will review all of the endothelial cell data analysis and when the Chair is ready, I'll be happy to project all questions as they appear in your handout.

DR. GRAY: Good morning. My name is Gerry Gray. I'm the team leader for cardiovascular and ophthalmic statistics and I was the statistical reviewer for this PMA. My comments are going to be restricted to the specular microscopy sub-study. This is an overview of the design. We've heard it several times. We're talking about endothelial cell counts and measurements on endothelial cells based on

photographs from a specular microscope and all the images were read at a core center with one reader.

The study was originally designed to have a preoperative and then three-month, one-year, two-year follow up. During the course of the study it was modified to add three and four-year visits. And the purpose was to investigate the effects on endothelial cells. There were a total of 306 eyes that were enrolled in this sub-study and it had at least one count. I'm just going to go through a little bit about the accountability of the eyes because it gets a little confusing here.

The pattern of missing is not quite standard where everyone has a preop visit and then people start to drop off after that. It's a fair amount different. In fact, there were -- 94 of the 306 patients had no preoperative visit. Six people had preop and one subsequent. Thirty-four had preop, two subsequent and 172 had preop and then three of them were after that, and the small numbers after that tell you where the person's last visit was.

And all this accountability information is

based on a data set that was submitted to me by the sponsor for analysis. So actually, I think it was a SAS formatted data set. A couple of more accountability combinations; 154 patients had preop and three-year visits, 57 comes up a couple of times. It's not the same 57 patients but 57 had three and four-year visits, 57 had preop and four-year visits. A total of 67 people had all the visits up to three years and a total of 37 had all visits up to four years. So there's 37 patients out of these 306 that had all the visits.

So here's a plot that we've seen before. It's the raw results from the data -- from the study, excuse me. The year or the time has been jittered a little bit to show the distribution there. There are preop measurements and then three months, one year, two years, three years and four years. The dashed blue line here just simply connects the means at those time points. And when we look at this, there's really two questions that are key here. The first one is how -- at what point in time can we say that any effect of the actual surgical procedure, whether it would be

just lost due to surgical trauma and/or some amount of remodeling, at what point in time would we say that is negligible and we can ignore it and use the data after that to get some estimate of what long-term loss might be? So that's the first key question that we need to think about.

And then the second thing is what happens off to the right-hand side of this graph, what happens after five, 10, 20 years down the road? Just to set the stage a little bit, this is -- these numbers here are the mean cell counts for various cohorts of patients that you might think about using in this study. The first cohort is all eyes. That's just all 306 eyes that were measured whenever, the baseline preoperative measurement, the mean was 2657 and it steadily declined after that to 2355 at the four-year point.

The next cohort, I couldn't fit it in very well, so I call it pre and two plus. Those are all the patients that have a preoperative measurement and then they had at least two measurements after that. So that's 206 of the 306 patients and you can see

there, it's fairly similar actually to what we get with all eyes. The next two cohorts are somewhat different. The cohort that only has three and four-year measurements and this is a cohort that in the analysis presented to us by the sponsor for the three to four-year loss they used. You'll note that the main difference here is at the three-year point that measurement of 2355 is somewhat lower and it's actually in fact, lower than the average measurement they got at four years for those 57 patients.

And then finally, an even smaller subset was everyone who had all the visits and that shows a similar pattern to the three and four-year one, and I presume these are the numbers that were used to make that plot that came up in the sponsor's presentation. So over the duration of the study, over the three and four years we're talking about here, the estimates of cell loss are fairly stable regardless of how you calculate them. At three years, the range of estimates is 8.5 to 8.9 percent. If you use the 154 patients who had preoperative and then three-year -- a three-year visit, the estimate is 8.7 percent. And

the competence interval for that is anywhere between a 10.3 and 7.1 percent loss. In raw numbers that's 220, 235 cells per millimeter square and that calculation includes anything that happened to the patients between preop and the three-year point which would be any initial operational loss, any kind of remodeling, any normal loss due to aging over that period.

And at four years, we've added on a little bit here and it's anywhere from 8.4 to 9.7 percent loss. Okay, now the big question, of course, is what's the steady-state long-term loss that we can expect to see. What's the long-term rate of change in the endothelial cell density we might think we would see? And it turns out that this estimate depends mostly on those -- on the question of how long we believe the effects of the implantation persist, at what time point can we say whatever remodeling or operative loss we have seen in negligible at this point. And that translates into which of the cohorts we actually used to do that estimation. As you saw in the previous slide, the table of cell densities, the

two cohorts on the bottom that only had -- that had three and four-year measurements had a markedly lower three-year cell count than the others and that's the main difference in terms of what you get out in the estimates.

The analysis that was presented to us by the sponsor in this PMA was basically using the percent change between the three and four-year time points, using only those patients who had both three and four-year measurements. That's the 57-patient cohort and it properly did some statistics to account for a correlation within a patient between eyes. And the net result there is an estimated percent change of .07 percent, that is a slight gain. In fact, it was one cell per millimeter squared with a confidence interval between minus 1.4 and positive 1.6 percent.

Now other cohorts you'll recall, have relatively higher three-year counts and you can do a lot of different kinds of analyses but the bottom line is that the various analyses using those other cohorts and using all time points or time points other than just the three and four-year, produce a change of

around minus two percent per year. If you go the fancy statistics route and do random coefficients regression, you get a loss of minus 1.9 percent per year. If you believe that whatever -- that the time cutoff for the operational and/or remodeling change is three months and just use the data after three months, and go through an analysis, it's exactly like the one done by the sponsor, in other words, just use the changes from time point T to T plus one, you get an estimate of minus two percent per year.

If you believe that any trauma or remodeling is done after two years and you use the two to three-year difference plus the three to four-year differences, you get an estimate of minus 1.8 percent. And the confidence intervals change a little bit. The one for the -- using the regression is probably the smallest because it has a model to help it make the balance smaller, but those are fairly consistent estimates compared to the difference between them and the one that only uses the three and four-year data.

So the key question, of course, is where is that cutoff between operative and/or remodeling

loss and whatever you might call steady-state, long-term loss. And all I can do is statistics, right? I don't have the clinical knowledge but I have the data, so using the data that we do have, the question here from the statistical point of view is we see that there's some amount -- in many of the cohorts, there's some amount of leveling off after the three-year point between three and four years and the question is, is that statistically significantly different than whatever the slope we saw between three months and one year, one year and two years, two years and three years. And the answer to that is no. If you'll recall the previous plot, it showed the dotted line that connected the means, it looked pretty much like a straight line and the statistics confirm that. There's no strong evidence that the rate of endothelial cell loss between three and four years is any different than the rate -- the annual rate before that. So in the data we have, there's not strong evidence that it's different. Of course, we only have 57 people at four years and that could be do to just random fluctuation or we just don't have a big enough

sample at four years to have much statistical power but that's what we have.

And just in case you care about the details, this was all based on a piecewise linear model that assumes there's a preoperative loss between zero and three months and then after that, it's steady decline either to three years and then a change to four years or it's straight from three months on. But the implication of all this from the data we have is that is that the steady state loss should be estimated using all the data after three months. And if you'll recall from a previous slide, even if we want to go to two years, it doesn't make that much difference here.

And so my best guess is due to long-term loss would be that we have -- first of all, there's a mean preoperative measure of 2651 and with the first three months, the absolute loss is about 1.9 percent, so about a two-percent loss over the first three months, and then after that, the rate of loss per year is about 1.9 percent.

If we extend this model a little bit to

include a three and four-year slope, which again was not warranted by the statistics probably, you do get a pretty similar estimate to what the sponsor had between three and four years of an actual slight gain. So here's the results from the two different fits, the two main different kinds of fit that I'm talking about. First of all, there's a blue line here that's just like the one you saw in the previous plot that's pretty much overlaid by the black line. The black line is the fit that I was describing where we had a linear drop at the three months and then a straight line after that. And the green line out at the end is the analysis that was presented to us by the sponsor which is just using the patients who have three and four-year data. And you look at this plot and you say, well, that's not that much different because you know, the only thing different is maybe the difference between the mean at three years there, but the problem is that we don't really care that much at the four-year point. What we care is what happens after 10, 20, 30 years and when you make the plot -- when you show the time span we're talking about those are quite

a bit different results.

And if you believe the three to four -- using the three to four-year data, we're basically a flat line, slight increase over time on the endothelial cell density. If you believe that the loss is going to continue linearly at 1.9 percent per year forever, then after about 20 years you're at the 1500 cells per millimeter squared and somewhere around 35 years you're down to 800. I don't have any -- I don't show any errors around these lines, in the error bars. If you know much -- if you know about errors for regression the errors go, they move outward the further away you get from the center of the data and if I put them on here, they would -- these estimates are pretty much meaningless I think after 15 to 20 years. You don't have very much confidence at all in them.

And that brings me to, of course, the caveats that the statisticians always give about extrapolation. It's always a questionable exercise to extrapolate beyond the range of the data we have and especially when we're talking about the range we have

here. It's highly -- any extrapolation you would make would be highly dependent on the model we use and the assumptions we want to make and both those lines that you saw previously assume that whatever linear trend you saw between three and four years is going to continue forever beyond that.

And it's probably in this case a lot more important to think about if it's necessary to obtain good long-term data and if so, how to go about doing that. Okay, now, I'm going to switch gears a little bit and talk about individual patients because maybe more important than the average cell loss through time which is described by the linear fits are questions like what proportions of patients will show a cell loss greater than some critical amount. In other words, what proportion of patients will have cell densities less than 1500 or 800 cells per millimeter squared in 10, 20 or 30 years.

And from my point of view, the problem is you can't really answer this with much confidence using the data we have here. But let me just summarize what we do have here. If you'll recall one

of the previous -- the fancy statistical model I used previously actually gives me an estimate for each eye of what the post-operative ECD change for that eye is and then after that, what's the annual change through time, and so you have a distribution of those estimates for each eye.

And using that, you can get -- you can create tables like this that tell you something like in this case four and a half -- excuse me, 10 percent of the patients will have an initial loss of four and a half percent or more and 10 percent of the patients will have an annual loss of 2.9 percent or more. Now, that's based on again, I'm making some assumption that whatever we've seen in the first three or four years is going to continue however far in the future you want to go. Okay, and finally, there were some co-variants that seemed to be significant predictors of endothelial cell loss, notably is the anterior chamber depth which was a statistically significant predictor of cell loss regardless of how you analyze it really. The sponsor presented analysis in the PMA that showed the used binned data, in other words, they

broke the ACD into four different groups based on three, three and a half, four millimeter cuts and then presented the cell loss for each of those groups.

A bunch of other co-periods didn't appear to be significant predictors of cell loss. Just to help put the ACD effect into context, I created this graph here that takes -- for each eye, you take all the possible annual differences that you got for that eye and calculate from those the percentage loss for that eye and then average those for that one eye. So on the Y axis is for each eye now an annual percentage ECD change that we see in the four years -- after three months. I threw out the first few months because that seemed to be somewhat different. And then platted on the X axis is the ACD measurement for that eye.

And the point is that, remember the average ACD is around 3.5 and the average cell -- annual cell loss was right here, it's around two percent and down here it says estimated slope is 1.6, so you know that the difference between -- if this right here is about two percent loss, and someone

that's a half a unit to the left is going to have a loss that's about 0.8 percent more, 2.8 percent, and someone who is a half a unit to the right is going to have about 0.8 percent, less cell loss. They're loss is going to be about 1.2 percent per year. This is just an attempt to kind of put the -- take the statistical significance of the ACD effects and try to put it in some terms that might be hopefully relevant.

So after all that, there's two main questions here for the panel. The first one is that the mean change between three and four years in that 57-patient cohort that had both of those was an actual gain of .1 percent in endothelial cell density, so is there sufficient data to support the conclusion that the losses in the first three years are reflective of surgical trauma with some prolonged remodeling period that culminates in a stabilization after three years and if not, what minimum eyes in follow up would you try to make a recommendation that we might need to make that assessment?

The second question relating to the anterior chamber depth eyes with the smaller anterior

depth of 2.8 to 3 had a greater loss of endothelial cells than the eyes with a greater than 3 millimeter ACD. So the question is, do the outcomes of the ACD analysis provide some assurance of safety in this device for eyes in the lower end and then the upper end of the ACD spectrum? Thank you very much for your attention.

DR. WEISS: Thank you. We will now have questions for the FDA from the panel. I'm just going to start off, just to clarify for myself about the endothelial cell loss in terms of determination whether it levels off or increases between three to four years versus whether it continues dropping. From what I understood you to say, if you look at the cohort of 57 which is what the sponsor was looking at between three to four years, you could possibly say that it was going to level off, but if you look at the other cohorts, it does not show that. Am I misinterpreting it or is that basically --

DR. GRAY: That's correct. Your estimated amount of endothelial cell loss depends primarily on which cohort you use and the one cohort -- the cohort

that has either the three and four-year measurement that has three and four-year measurements has a lower three-year count and therefore, you get basically a flat line after that.

DR. WEISS: So we have a choice of basically looking at the cohort of 306 and if we look at the cohort of 306, it does not support leveling off between three to four years. If we look at the cohort of 206, it does not support leveling off at three to four years. And if we look at the cohort of 37?

DR. GRAY: Well, when you say "support" it might mean a different thing to you than to me. When you get down to the 57 or 37 patients, there is more of a leveling off but on the other hand, there's more air because you have fewer patients. So I didn't actually do the test with the 37 patient cohort, but my guess is that you couldn't say statistically that there was a difference, but I didn't actually do that.

DR. WEISS: But certainly for the larger groups, which would have more statistical strength, it shows no leveling off.

DR. GRAY: That's correct. I personally

used -- concentrated on the group that had a preoperative measurement and then two or more measurements after that because that was the one that I -- in order to do these tests you have to be able to fit a model of some sort.

DR. WEISS: So we're talking about if you look at the group of 206, which had the preoperative measurement and measurements at each of these time points, or at some of these time points, at least on two.

DR. GRAY: Two or more, yes.

DR. WEISS: At two or more of those time points. If you looked at that group, this did not support leveling off between three to four years.

DR. GRAY: From a statistical point of view doing the test for leveling, that's correct, it did not support it.

DR. WEISS: Okay, thank you. Dr. Grimmett?

DR. GRIMMETT: Michael Grimmett. Dr. Gray, I appreciate your comments. On the group of 37, you may not have run the analysis at the end but did

you calculate the rates of or the confidence intervals for the endothelial cell loss, what it ranges between for the 37 eyes at year four? Did you show that? I mean, I know for the 57 it was a 90 percent confidence interval was 1.4 something. Did you do the same thing for the 37 eyes? It's probably wider, right?

DR. GRAY: No, I didn't do that. It would most likely be wider because of the sample size is three-quarters. So that would increase it by some amount, yes.

DR. GRIMMETT: Okay, thank you.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: Dr. Gray, on one of your last slides there you showed us the relationship between anterior chamber depth and cell loss and you did a linear regression that 1.6 percent per millimeter.

DR. GRAY: Yes.

DR. BRADLEY: Did you do the analysis to find out how much of the variance was explained by the linear model? That becomes quite an important number for us.

DR. GRAY: Well, that was part of the analysis but I don't have that number here on me. The reason I -- I guess their point is that there is a statistically -- when you ask how much of the variation is explained, there is a statistically significant -- that slope is significantly different than zero, okay, so from a statistical point of view there is -- that's a significant slope. And what I was trying to get at was that what's the clinical relevance of that and that's where -- why I made the plot that calculated the 1.6 percent per year. But I don't have that number on me.

DR. BRADLEY: Yeah, but it's the clinical significance that's driving my question here in a sense that the linear regression might be highly significant but it may explain a very tiny amount of the variance and thus making policy based upon a parameter which explains only a tiny amount of the variance is really meaningless. So if we had that number or after the meeting somehow that number could be available, that might help policy.

DR. WEISS: Dr. Bandeen-Roche, Dr.

McCulley and then Dr. Mathers.

DR. BANDEEN-ROCHE: Thank you for your presentation. I just have a brief clarification question which is that the numbers that you cited for the four-year mean cell counts differ from the calculations that I cited earlier. And so for instance the three, four-year mean that you cited three years and four years is 2355 and 2356 and reading from Volume 4 of 4, page MD19, those numbers are cited as 2455 and 2456. Now, this in a way sounds like a little point but it goes to the representativeness, the relative representativeness of the various cohorts. So I don't know whether it's clear which one of those is right.

DR. GRAY: I'm not, those all differ by exactly 100?

DR. BANDEEN-ROCHE: Yes, yes.

DR. GRAY: So my first guess is somebody has a typo because that's probably not just a coincidence that they're both exactly 100 off. These calculations that you see here, the mean cell, the sponsor sent me a data set at the end of July, July

25th, that has the endothelial cell counts that I later discovered they were rounded -- these are mean so they were rounded off to the nearest cell, the one I got. And that -- the numbers you see here are what I calculated using the data set that I was sent.

Now, if the three and four years -- if the two-year number is correct of 2428, then I would say 2455 and 2456 are probably not correct, because that would mean that there was an increase between two years and three years as well.

DR. BANDEEN-ROCHE: Okay, thank you.

DR. WEISS: Dr. McCulley?

DR. McCULLEY: Yeah, I've already expressed a little bit of skepticism about the emphasis being put on cell density but I know those are the numbers you had when you did your analysis, but from a clinical standpoint just over the years, I'm a little skeptical about putting too terribly much weight on something that can vary depending on where you take the count and the variability over time, the reproducibility, so I remain a little skeptical in that regard based on my clinical experience and what

I've seen in reviewing papers and hearing presentations over many years.

So I guess then my question is, did you do any statistical analysis assessing the size and shape variation over time of the cells?

DR. GRAY: No, I did not do that. I used the results that we were submitted to us by the sponsor which seemed to indicate there was really not an issue. So I didn't --

DR. McCULLEY: Not, an issue, I'm sorry, meaning what, that there wasn't a change over time?

DR. GRAY: There did not seem to be a change through time for either the percent hexagonal or the CV and I didn't dig into that further. I used the same thing that you got in the submission, which is the analysis that the sponsor did.

DR. McCULLEY: Yeah, I mean, in the absence of data, I don't really know for sure what's right here and your extrapolation caveats, I think, are good and it would be nice to have the very long-term data, but at least from a cell density standpoint, my impression is that the critical cell

density for corneal edema is 800 plus/minus 400 roughly tremendous range and tremendous variability. And that these other factors seem to play a very critical role and it would be more comforting for me to know that we had more data to support the size and shape didn't change over time. The numbers just aren't -- or the density isn't the only thing and there's tremendous variability in the measurement methodologies.

DR. WEISS: One thing, and I hope that we can pull this perhaps on the lunch break is one difficult item is for the August 2002 panel meeting when we had some of the people who were working with sponsor actually consult and guide the panel as far as what the requirements should be for such a study, I do not recall any such emphasis on hexagonality and coefficient of variation. The number -- the cell density is what was emphasized. Dr. Grimmett can comment in terms if your recollection is any different.

DR. GRIMMETT: Yeah, Mike Grimmett. I was the assigned primary reviewer for endothelial analysis

at that meeting in August of '02 and in the presentation I made and included in the outline were the references that Dr. Edelhauser was citing regarding the sensitivity of pleomorphism and polymegathism so it was covered. I don't think the sponsor emphasized it or the presenters emphasized it but I did cover it in my presentation, making very similar comments to what Dr. Edelhauser said.

DR. WEISS: Dr. Mathers?

DR. MATHERS: Thank you for the clarity of your presentation. I thought it was very helpful. In the written work that we were given beforehand, you note that the -- by your model one you had an endothelial cell density loss in absolute numbers of about 49 cells per year and 20 percent of the population actually had a cell loss of 100 cells per year. That's what you're saying. Am I correct in assuming then that that 20 percent of the population in this population would then have an endothelial cell loss rate of about 3.8 percent per year by that calculation? If the 4.9 is average and the average is 1.9 by your model 1, it seems to me that would give a

20 percent of this group that were having a loss of 3.8 percent per year. I mean, that's the logical conclusion.

DR. GRAY: That is a conclusion that I didn't actually calculate. It's very difficult -- the problem is it's hard enough to estimate the mean function here and now we're trying to estimate the line below which only 10 percent of the people are going to be. And that actually is not -- is even harder statistically.

DR. MATHERS: Right, okay.

DR. GRAY: The best estimate I can do right now, based on the data we have are what I gave in the presentation, which is that 25 percent of the people will have 2.3 percent or more. Now, if I understand your confidence limits on that, it would be pretty wide.

DR. MATHERS: Right.

DR. GRAY: I'm not sure exactly what they are. I haven't -- I don't have them on me.

DR. WEISS: Seeing no other -- Dr. Macsai?

DR. MACSAI: I have three brief comments

and I thought all your presentations were great, thank you. The first, they all revolve around endothelium but the first is to Donna. In all your presentations about ANSI and the guidance documents, nowhere did you mention a history of contact lens work and in light of all this discussion about endothelial cell remodeling, I would ask the agency to consider adding that so that that -- I think it's a critical piece of information to help us in the future on any intraocular device.

So I didn't see it. Maybe it's there.

MS. LOCHNER: It was discussed at some of the earlier panel meetings and the end result was that I think given considerations to the population you're treating and that there is going to be contact lens wear and what's the practical thing to impose on a clinical study, in the end the panel didn't give that emphasis, but I do hear what you're saying and I appreciate the comment.

DR. MACSAI: I'm simply asking for history so that you could segregate out --

MS. LOCHNER: Oh, yes, yes.

DR. MACSAI: -- who wore lenses and who

didn't preoperatively. It helps analyze this endothelial cell data.

MS. LOCHNER: Yes, and I think many studies will be able to do that.

DR. MACSAI: Okay, the second two questions are for Dr. Gray. In this data set you received from the sponsor, do you know if patients who had exchanges at the time of implantation or subsequent to the time of implantation were excluded because that would skew this data, I think significantly?

DR. EYDELMAN: I think I actually touched on this in my review. I believe there were two different analysis. In the overall analysis by the sponsor, the data for the eyes that underwent secondary procedure were included, but they were excluded in the analysis where they were determining ACD significance.

DR. MACSAI: But were they excluded in measuring endothelial cell density long term?

DR. EYDELMAN: They weren't excluded from continuation of collection of data if that's what

you're asking. We don't have the analysis for those eyes separated out.

DR. MACSAI: Well, do we have an analysis of the eyes that had the lens put in once and only once and never touched again and what happened to the endothelial cells?

DR. EYDELMAN: I believe that would be the analysis where the tables for the ACD depth significance were performed.

DR. MACSAI: And then I would ask Dr. Gray, looking at those tables, does your slope still hold to the green versus the black slide number 15 or whatever it was, 13, sorry?

DR. GRAY: I guess I'm -- first of all, I'm not entirely sure because I don't recall the exact -- I didn't actually do that analysis both ways to compare but the key difference between the estimates that we saw was the fact that the 37 or the 57 patients had a lower, a much lower count at the three-year time point than the other group and that's what is driving most of the difference. All the other methods of analysis and different groups of patients

that you include, if you get beyond just the three and four-year data, you have a switch and so all of a sudden, it's about two percent, 1.8, 1.9, 2 and so it really comes down to a question of what time point you think the remodeling is over or whatever happens during the surgery is done with and beyond that, we can consider steady state. And then you get into the whole issue of what does that even mean and how can we extrapolate 20 years down the road which is sort of unanswerable, I think, with the data we have.

DR. MACSAI: Maybe I'm not getting something here.

DR. EYDELMAN: Let me just try to add, we don't have exactly what you're asking for, Dr. Macsai. We don't have the analysis of just the eyes that had secondary intervention, the endothelial cell separated out. What I do want to point out were that there were few eyes to start out with and chances are some of them did not have the analysis all together. As far as I'm aware, PMA did not contain breakdown for the -- on this issue. Certainly your recommendation can look upon it after the panel.

DR. WEISS: Since we're running 40 minutes behind and we haven't gotten into a discussion, I'm going to have one brief comment by Dr. McCulley, and then we're going to go to five minutes of questions for the sponsor and then break for a 45-minute lunch.

DR. McCULLEY: Okay, a critical question seems to be in humans, how long does it take for the endothelium to remodel after an injury and is it degree of injury dependent, is it age dependent? I don't know the answers to those questions but that seems to be absolutely -- the answer to that seems to be absolutely critical in knowing how to interpret the cell density and the cell shape and size change. Do we know that? Do we know how long it takes to -- and maybe when the sponsor comes back, Hank will know. But that's a key question to all of this.

DR. WEISS: I want to thank FDA for an excellent analysis and presentation. Sponsor, would you be able to answer or address some of these issues? So you have five minutes to answer all our questions. While the sponsor is setting up, when we break for lunch, I'll just point out, this will be abbreviated.

It will be 45 minutes, not an hour as listed in deference to the fact that we are running over significantly at this early point in time.

MS. THORNTON: Are you ready, Dr. Vukich?

DR. VUKICH: Pardon me?

MS. THORNTON: Are you ready?

DR. VUKICH: I believe so. For some reason, I believe the projector was changed out from underneath us. Okay. We would like to just take a moment to respond to a couple of the questions that were requested of the sponsor. For the number of sites that were contributing to the four-year analysis, this data was collected at eight of the nine sites that were collecting specular micrographs. We were able to calculate the confidence interval for the 37-eye consistent cohort of eyes at all of the intervals and that will be the graph that follows.

There was clarification that we will need from Dr. Bandeen-Roche on her request for information on an overlie of one of our cohorts, but it may take a little more time than we have available and a little more clarification on exactly what we would like to

provide. This is the 90-percent confidence interval of the mean for the 37-eye cohort and at four years, which I think is the point of interest. It was 2244 to 2509. I see we're taking notes here. Okay, good. This is the entire cohort then for the endothelial cell density. For a point of clarification, this cohort did include all patients and these were also -- who were examined and did include patients who had secondary procedures so in some essence it does look at a worse case scenario.

A separate analysis of the data, subtracting those patients out has been done. We can tell you that it shows no difference in our estimation. We were hoping it would, but it didn't.

There was one final question that we'd like to address and that was from Dr. Bradley. There was a question concerning pupil size and quality of vision. We wanted to point out that our contrast sensitivities were all done under mesopic illumination at 3 candelas per meter squared. Although we did not have pupil size to correlate with that, there would be some assumption that the pupils would be at least

smaller than under photopic conditions and that with and without glare there was no demonstrable difference at post-operative contrast sensitivity and in fact, at four of the five measured intervals, there was actually an improvement in contrast sensitivity so we hope that speaks to the quality of vision at least under mesopic conditions.

Finally, we'd like to thank the members of the FDA panel for their thoughtful and thorough review of all of this information. Thank you.

DR. WEISS: Thank you for making it brief.

DR. McCULLEY: Does Hank have an answer to my question?

DR. WEISS: We'll find out. Can you make it -- can you give a brief answer and if the answer is, we don't have the information, then that is the answer.

DR. EDELHAUSER: I think that is the answer. We don't really have the information. The only really data that we can rely on is probably the keratoplasty data from Bill Bourne which showed a market drop-off, you know, and that's not really the

data we're after. So we don't have the data.

DR. WEISS: No data. Forty-five minutes for lunch and then we'll be starting promptly.

(Whereupon, the proceedings in the above-entitled matter went off the record at 12:22 p.m. and went back on the record at 1:14 p.m.)

DR. WEISS: Can everyone from the panel take their seat, please. We're going to continue the Committee deliberations on this PMA with presentations from Primary Panel Reviewers, beginning with Dr. Marian Macsai-Kaplan. I will remind Panel Members and Sponsor, and FDA, et cetera, that we are now about an hour behind, so I would suggest or request that all comments be short, to the point, and have the purpose of moving this PMA ahead.

DR. MACSAI: I'm done.

DR. WEISS: With that non-intimidating introduction, I have Dr. Macsai.

DR. MACSAI: I would like to first acknowledge a few things. One is, that the Sponsors did an amazing job on a really fast track PMA, and that the FDA did an outstanding job in getting us this

information as fast as it could be gotten. And I want to really thank Sally for being in such close communication. This was a difficult PMA to review I think for all of the reviewers.

The Sponsor has gone through a lot, and so has the FDA, so I'm going to try and limit my comments, but I have a few things I just feel obliged to say.

First of all, you saw in the distribution of the patients enrolled in the study, that the vast majority were Caucasian. And from previous devices we looked at, we realized that we do need to look at the affects in non-Caucasian patients. The Sponsor did supply data from the Dominican Republic data set, and I think it would be important for that to be included in anything made available to the public, segregated by refractive error, to help the non-Caucasian population with their expectations.

Second of all, exclusion criteria were included, and 65 eyes with pre-existing conditions were included in the study. The results of what happened to those 65 eyes should also be made

available by the Sponsor to the Agency, because from those 65 eyes, we may glean information that would help patients who might be treated in an off-label manner.

In addition, in the exclusion criteria, limbal pathology was not included, and must be included if a white-to-white measurement is required to size this IOL.

Another additional criteria that must be included for exclusion is what the lower limit of endothelial cell counts are per age group. And I would reference Dr. Grimmett's excellent review for that.

I'm going to now address efficacy, and then the questions put forward by the Agency. Efficacy of this device is really good, very good. And I'm going to just limit by comments by saying that I was happy to see the efficacy of this data in the 3 to 7, 7 to 10, and 10 to 15 diopter groups, and leave the over 15 diopter group for later in my discussion.

I would have some questions why a refractive surgeon might use this in a minus 3 diopter

group, and until I personally see data that this is superior to refractive surgery already out there, I would personally wonder about that issue.

Regarding the specular microscopy data, which was my question 1 in the original questions provided by Dr. Eydelman to us, I feel uncomfortable, plain and simple. I feel uncomfortable because we haven't set a limit of what is the minimal number of endothelial cells that a patient needs to have. We're talking about implanting a device in a 22 year old patient, taking worse case scenario, as the Sponsor said earlier.

We've segregated out the patients that had complications, replacements, removal, and if you take a 22 year old and assume that they don't become in need of a cataract until they're 62, assuming they're myopic, they have a higher prevalence of nuclear sclerotic cataracts, you're talking about the device remaining in place for 40 years. And at 40 years, according to Dr. Gray's chart, they're going to drop to a dangerous limit. And so my discomfort comes from the fact that the surgeons who participated in this

trial are the best of the best. They have the best hands, they have the best experience. I've had the privilege of being taught by some, and observing them, and they are really the best there is, so we're taking a device and releasing it to Joe Q. Average surgeon, and this device will be seen as sort of a drive-through procedure, I'm afraid, where you drive in, you get your IOL, you drive out, you move to Outer Mongolia, and we don't know what happens to you. And we don't know what's going to happen in 10, 20, 30, 40 years to the endothelium. So I, of course, having experienced the closed-loop AC IOL induced pseudo phakic bullous keratopathy, am concerned about this device and its effect on the endothelium. And that, to me, is the biggest issue with this PMA. Everything else is really pretty small in comparison to that.

Along those lines, we were asked to look at the anterior chamber depths. And I think the Sponsor has shown, Dr. Gray has shown, everyone has shown that in the hands of the best, with an anterior chamber depth less than 3, this device induces a 50 percent higher endothelial cell loss. So at this

time, my recommendation would be that this device not be labeled to be used in an eye under 3 millimeters anterior chamber depth. And that if the Sponsor has further data, that can, of course, be looked at in the future.

Question 2 is the nuclear opacities. Nuclear opacities in this population developed at two time courses, early-on, probably surgically-related. Later on, probably nuclear sclerosis developing in these high myopes.

I didn't have a big problem with this, but it brings very much to the surface the training of surgeons who are going to use this device. If you look at the Canadian data in those three inexperienced surgeons, there was a 22.5 incidence of anterior subcapsular opacities, while the surgeons that were proctored in the Dominican Republic only had a 4.8 percent incidence of anterior subcapsular opacity development. So clearly, that technique used in the Dominican Republic has some effect, so the Sponsors are now left with a huge challenge; how do you take Joe Q. Average surgeon and make him good enough to use

this device?

And some of my suggestions would be that this device, this Collamer ICL is very similar to the Collamer posterior chamber intraocular lens and Toric intraocular lens that is currently available, and has been for years, for cataract surgery. And that any surgeon who wants to implant this device must first become proficient using that intraocular lens and loading it in the shooter, which is the exact same, and implanting it in the eye. And only after they're proficient with that device, should they then be able to use this device. And they should be proctored one-on-one in the use of this device.

But it brings to mind another concern, which is, if you look at the analysis of the investigational sites, one surgeon at one site had a significantly higher number of complications, and a significantly higher number of IOL removals and exchanges. And remember, we're dealing with the best of the best, so I raise this question to the Sponsor, pending release to the general public, how is the Sponsor going to monitor this? If the Sponsor has to

supply these IOLs to someone who's exchanging them too often, or repositioning them too often, the Sponsor seemingly should have some kind of tracking method for this, and further training required prior to the release of this device. And it's a big, onerous task, but we're talking about putting this in young people with clear lenses, so I think that there's a degree of responsibility the Sponsor will have on this post-approval.

Regarding the Agency's question about removal, and if there's areas of touch, and if the uncorrected vision is worse than 20/50, I thought these were fine caveats, but I would also raise the question to both the Agency and the Sponsor, if there is an anterior subcapsular cataract in the visual pathway, should that also be added as a reason for removal?

Question 3 regarded the use of the horizontal white-to-white in the anterior chamber depth measurements to determine the sizing of the ICL. I too, like Dr. Grimmett, went back to my operating room and looked at what I had available to measure

white-to-white, and it's just a little, I think, Castroviejo caliper, and mine goes by 1 millimeter increments.

I, like Dr. Vukich and Dr. Slade, was trained in a time that we did extra caps, we measured white-to-white. I think my residents have done five extra caps in their entire training. I don't think they know how to measure white-to-white. I think the Sponsor is going to either have a huge task of teaching them how to do it, or find a better technique. And for that, I would recommend consideration of the Orbscan, which we now know has been shown in the Wang article from the Development of Ophthalmology Journal to be reproducible. It also supplies your anterior chamber depth.

I'm not endorsing that product. I hold no interest in that product, but it's out there, and it would give a reliable reproducible measurement for the beginning surgeon. Regardless though, if the patient has limbal pathology, you cannot ascertain a white-to-white measurement; therefore, that is an exclusion criteria in my mind for this device.

Question 4. There are currently no devices approved in the U.S. for correction of myopia greater than 15 diopters. True. So I feel once again very uncomfortable here.

First of all, clearly this device in that population does not correct myopia, it only reduces it. So in light of Dr. Eydelman's question, we have to change "correction of" to "reduction of". But I worry that we, as a panel, are going to arbitrarily set a standard by approving this in this age range.

I look to the Agency, and ANSI in their wisdom for guidance, and my feeling is once a guidance document is developed in this population, minus 15 to minus 20, and the Sponsor has this engineering thing worked out, that at that time, once the guidance document is set, if the device meets the guidance document criteria, approval is a no-brainer. But at this time, we have no guidance, and I'm uncomfortable with arbitrary approval, which would set a standard, because I am certain there will be more phakic IOLs to come in the future.

Question 5, does safety and effectiveness

data support approval of the STAAR ICL for the eyes with the following pre-operative MRSE, minus 3 to minus 7, minus 7 to minus 10, minus 10 to minus 15. And in general, my response to this question is yes. However, there remains this outstanding issue regarding endothelial cell loss, sizing of the IOL, cataract information. I'm not uncomfortable with the cataract formation, sizing of the IOL is fixable. And I guess I feel if Dr. Edelhauser doesn't have the answer for endothelial cell loss, I don't know who will. And so, we're functioning in a big old gray zone. And maybe a warning that might be appropriate is that endothelial cell count must be done on these patients pre-operatively, and should be done on these patients post-operatively for a very long time. And if there is a decrease long-term in endothelial cell count, not from an otherwise obvious condition, such as a high fema, trauma, iritis, that perhaps this device should be explanted to protect these patients from pseudo phakic bullous -- from bullous keratopathy at some time in the future.

The Sponsor Question 6, management of

acute intraocular pressure rises in post-operative period. Well, I'm disappointed that gonioscopy was not performed post-operatively in these patients, and I think that Dr. Lochner's presentation has addressed this issue. A mistake was made in the development of this PMA protocol, and it will have to be rectified in the future. But perhaps if the PIs were made farther in advance - I don't know, one week seems awfully early to me - the PI would have healed, and not of them might have been included. And there wouldn't be a need for reopening in the future.

In addition, I think the Sponsor must mandate that the surgeon check the pressure within 4 to 6 hours after placement of the device, and again in 24 hours, so that if it's the viscoelastic, this can be addressed.

Question 7, Sponsors have reported that a number of patients noted glare and/or halos post-operatively. Again, I'm disappointed because though Dr. Schallhorn might feel pupil does not make a difference, and I know this lens is much farther inside the eye, I think we could have learned a great

deal from that information. And I would ask the Agency to mandate pupil measurements in the future, so that our patients can have a better idea of what to expect from a device. Without it, we can't answer the question, so we're kind of left -- we need to include the data about glare and halos, what patients experienced. We need to include the data about the quality of vision pre-operatively. It was poor at 11.6 percent of patients pre-operatively, but at 36 months, it was still poor in 5.8 percent of patients. And that's a little disconcerting, because if you read the recently published paper where they compared an eye with an ICL and an eye with LASIK, those patients were doing great. And I have no doubt that the refractive quality with this device for patients will be better than a minus 10 LASIK. And that the higher order aberrations will be less with this device than a minus 10 LASIK. But I'm still wondering why 5.8 percent of the patients rated their vision poor. Who were they, and why was it poor? So that concludes my presentation. Thank you.

DR. WEISS: Thank you very much, Dr.

Macsai. We're going to have Dr. Joel Sugar, who's the second primary reviewer.

DR. SUGAR: Thank you. I'm going to just skip through various parts of my review. Of course, I want to thank and compliment the Sponsor and the FDA reviewers for the excellent job they did in both putting the data together, and then analyzing the information.

The accountability was good in the study. The efficacy was good up to the minus 15 diopter range, and beyond that range, certainly reduction of myopia should be the indication, or the labeling should be for reduction of myopia, not for correction of myopia. The stability was good.

In terms of safety, the loss of lines of best corrected visual acuity, I thought was very acceptable. I think that you can play games about the fact that the minification has changed and, therefore, you should lose less lines, but what matters to the patient is how well they see. And if they don't lose lines of vision, even though they should have theoretically gained a line of vision, I think they're

still benefitted.

I was concerned about the patients who required enlargement of their laser iridotomies post-operatively because of elevated interocular pressures. In my review, I had the wrong time periods because I measured from the baseline examination, not from the day of treatment. I'm concerned about the Sponsor developing a better means of assessing the iridotomies, both their spacing and their size, so that these patients won't have the pressure elevations as high as 65, as were noted in the presentations.

The retinal detachments, I think were acceptable given the population that was being assessed. The cataracts, I think, were acceptable given the population that was being assessed. Although I have concern about the recommendation for removing the lens when anterior subcapsular cataract is seen at an acuity of 20/50 or greater, I would be more concerned about removing it when there's progression of cataract. If, however, I had the data that I don't have, which is, is going in and taking the IOL out, putting a new one cause more progression

of the ASC or not, and I don't think we've been presented with any information to tell us whether that does or does not happen.

I'm also concerned in terms of the issue of cataracts, since these are patients who will develop cataracts in the long run, like all of us. Is axial length measurable through the IOL easily or not? Does a new algorithm have to be developed for ultrasonic, or whatever technique is used for measuring axial length?

People who have their axial length measured, their anterior chamber depth measured ultrasonically could presumably have that data, their axial length captured concurrently and presented to the patient. And it would, I think, make sense, since this is an implant, that the patients be given a card with the data on the lens implanted. But also, if there's data on their axial length, that that be captured, unless it's easy to measure their axial length with the IOL in place, and it would be nice to know that from the Sponsor. It would also be nice to know whether exchanging the lens in and of itself

induces another order of complications.

Endothelial cell loss has, I think, been very well discussed, and I guess I do feel that, contrary to what I wrote in my review, that anterior chamber depth less than 3 should probably be contraindicated for this lens.

There are a few other minor issues. There's some in the labeling that I mentioned in my review. For example, in the brochure it says that surgeons should never touch the center of the optic with instruments when it's in the eye. I don't know if that's because of concern about leaving imprints on the lens, or it's because pushing the lens, pushing the IOL into the crystalline lens could induce cataract. It would be worth having a statement in the brochure saying why that's an issue.

The statements made, again, in the labeling, that this device has "been shown to improve the overall quality of vision", I think that's too broad a brush to paint this with. I think you need specific data saying that some patients have overall vision improvement, some don't, and give data.

The brochure should also, I think, have a picture of the device, and a picture of the positioning so that even if someone's taking a course, they will have some hard copy information, should a question arise about lens positioning; although it seems pretty obvious.

In terms of the specific questions, is there sufficient data to suggest that there's remodeling? I think that there is. I'm concerned that we capture more data in four years, and definitely capture data at five years on endothelial cell loss. I don't think that we should wait for that information to approve the product.

I already talked about the anterior chamber depth. Do I believe surgeon experience is an issue? Absolutely, and that's been addressed by the Sponsor, saying that there will be mandated training. I also talked about the anterior subcapsular cataract, that we need more information on what secondary interventions do.

Do I believe the method for determination of overall diameter is appropriate? I think that it

is. I think that white-to-white is not as difficult to measure as has been implied. While Orbscan gives it a .1 millimeter on a standard printout, it gives you the white-to-white up to .1 millimeter, I don't think that that -- and that's been shown to be reproducible, I don't know that it's been shown to be any better than manual white-to-white measurements. And certainly, hasn't been shown with this device to provide any advantages. And it's a substantial expense for the average practitioner, who may not have the Orbscan.

We talked about the greater than 15. I think that the device should be approved for correction of myopia up to minus 15 diopters, and for reduction of myopia beyond that level. And I think that ends my review. Thank you.

DR. WEISS: Thank you very much, Dr. Sugar. The last reviewer, Dr. Grimmett.

DR. GRIMMETT: I'm pleased to have the privilege to make a few comments about the application. I apologize for any redundancy. I didn't have any of the talks before during the

preparation of my talk. Additionally, part of my purpose and mission is to get the information in the public record, so that interested patients in the future can search relevant issues regarding this device.

You've obviously all read my review, the cure for insomnia, and I will try to highlight just a few of those issues, but will not go over the data in excruciating detail. You can be happy about that.

Before I dig into the PMA, I'd like to go over a few background issues regarding the application to help us in our overall analysis. First, I want to review a few issues related to phakic IOL lens vault. Proper lens vaulting is clearly critical to the success of this phakic IOL. Excessive vault over the crystalline lens will push the iris forward, and has the following potential complications; angle closure, angle synechiae, iris chafing with potential complications of pigment dispersion and pigmentary glaucoma, iris sphincter erosion, iris translumination defects, and alteration of the normal aqueous dynamics that is pupilary block.

On the flip side, a poor vault in the -- over the crystalline lens has the potential to induce cataracts due to IOL crystalline lens contact. Moreover, if the IOL is too short, it's theoretically possible for it to be mobile, with possible rotation or anteroposterior movement. Clearly, the vault has to be just right to minimize complications, and the tolerances are expected to be low.

With an older version of the ICL, Version 3, the Sponsor believes that poor lens vault led to a higher right of anterior subcapsular opacities, quoting results from Sanders, in the Journal of Refractive Surgery in 2002. The current application states that Version 4 has an additional .13 to .21 millimeters of anterior vault, as compared to Version 3. And while I didn't find data in the PMA to substantiate that, the Sponsor clarified today that's a design issue.

In the literature, Gonvers & Associates examined central vaulting with digitized slit lamp photographs in 75 eyes. They had 24 V3s and 51 V4s. At three months, the central vaulting of the 24 V3s

was slightly less than the central vault of the 51 V4s, but the difference in their study was not statistically different. And they concluded, "The change in design between models V3 and V4 did not achieve its goal, which was an increase in vaulting." I just bring that up because I didn't see any data in this application to substantiate the assertion in vivo. Certainly, it's important to keep in mind that increased vaulting may reduce cataractogenesis at the expense of iris and angle complications.

In the application, when looking at vaulting, one gets the impression that the phakic IOL vault is a static situation, but I don't -- this couldn't be further from the truth. Stable phakic IOL vaulting on a day-to-day basis is probably not achievable for numerous reasons. Number one, accommodation has been shown to decrease anterior chamber depth by about a quarter of a millimeter, increase the lens thickness by .28 millimeters, and it decreases the radius or curvature of the anterior surface of the crystalline lens.

Number two, lens vaulting may differ,

depending on whether the patient is supine or prone; that is, gravitational effects. And number three, the light reflex has been shown to cause a reduction in the phakic IOL anterior capsular distance. Therefore, on a day- to-day basis, the actual lens vault is probably a dynamic variable.

Here's an ultrasonic image from Kim and colleagues in AJO in 1998. The third image on the top shows accommodation on a 30 centimeter target, and displays a decreased distance between the IOL and the crystalline lens right there, due to changes in lens thickness and radius of curvature.

The fourth image shows a relationship of the phakic IOL to the crystalline lens in total darkness right here. And then the relevant change when shining a penlight on this eye. In this particular case, there's IOL lens contact with simply a light reflex. Based upon these data, perfectly static phakic IOL crystalline lens relationships on a day-to-day basis are improbable.

Moreover, stable IOL vault over the lifetime of the eye is probably not achievable either

for numerous reasons. One, the soft IOL material may flatten with time. Dr. Vukich, I believe, mentioned European or outside the United States data over 10 years, that it may not. There is an article in the literature that indicates that it may. I believe it's from Arne.

Number two, aging has been shown to increase the lens thickness by 1.24 millimeters from age 40 to age 65. Number three, plate phakic IOLs may rotate or have mobility. And number four, the ciliary sulcus diameter has been shown to decrease by approximately 1 millimeter in diameter from age 40 to 80.

All of these day-to-day and lifetime issues may lead to intermittent or permanent IOL crystalline lens contact, and may lead to cataractogenesis, pigment dispersion, subclinical inflammation, and/or disruption of the normal aqueous humer dynamics. Given these factors, I can't imagine that ICL positioning will be stable and problem-free for the lifetime of a given patient, especially since this device is intended for young recipients.

Let's talk about issues related to the sizing of these IOLs. The sizing of the ICL myopic lenses was determined by the horizontal white-to-white and the anterior chamber depth measurements in the following fashion. For anterior chamber depths 2.8 to 3-1/2, they added half millimeter to the white-to-white, and for anterior chambers greater than 3-1/2, they added 1 millimeter to the white- to-white. For in-between sizes, there was a rounding down and rounding up protocol.

Hence, STAAR's sizing methodology is based upon white-to-white measurements. However, valid scientific evidence exists saying that white-to-white measurement do not correlate to the sulcus dimension. So white-to-white measurement does not -- is not a good surrogate marker of the variable of interest, the sulcus diameter.

Here is just one piece of information from Reinstein's study, in which he examined white-to-white values with calibrated photographs and sulcus-to-sulcus dimensions with high frequency ultrasound. All this information is in the public

domain. It's right off the Internet.

The top value shows that of myopic eyes, plotting white-to-white on the X axis, and sulcus-to-sulcus on the Y axis, that there's no correlation for myopic eyes. The same was true for hyperopic eyes.

These data imply that a one-size fits all phakic IOL would seemingly have just a good chance of success or failure as basing the ICL upon the horizontal corneal diameter.

Let's go ahead and look at a few examples of basing the ICL on white-to-white measurements to display this fact. Here's a case where white-to-white is 11-1/2 OU. Put the ICL based on that, bravo, it looks pretty good - adequate lens vault in both eyes, left and right, so we're pleased with ourselves on this case.

The next one we have an asymmetric white-to-white, 11-1/2 on the right, and 12 on the left. However, despite differing white-to- white measurements, the lenses were over-sized in both by about the same amount, rather than an asymmetric

amount, and the vault is excessive, causing angle closure, as you can probably see.

Here's a case where the same white-to-white existed on both sides, but the vault was excessive on the right, and non-existent on the left, with lens IOL touch. I simply would say that because there's valid scientific evidence indicating there's a lack of correlation between white-to-white and sulcus-to-sulcus, that physician labeling should include relevant material facts indicating the lack of the correlation. In fact, in knowing this data now, it's amazing to me that the vault data within the application is as good as it looks.

We'll review a few issues related to glaucoma. And please pardon me, Dr. Coleman. I will defer to your judgment on these issues. I'm just the cornea guy. Projected glaucoma risks for this device include pigment dispersion syndrome, angle narrowing, and angle closure.

Regarding pigment dispersion syndrome, it's important to realize that STAAR's study cohort fit squarely within the known risk factors for pigment